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The Influence of Various Pharmacological Agents on the Analgesia Induced by an Applied Complex Magnetic Field Treatment: A Receptor System Potpourri

L. J. MARTIN AND M. A. PERSINGER

Behavioural Neuroscience Laboratory, Laurentian University, Ontario, Canada

The opioid receptors have been considered one of the mechanisms by which the analgesic effects of 30-min exposures to temporally patterned weak (1 mT) magnetic fields are mediated. In 3 separate blocks of experiments, we explored the interactions between 2 examples of these magnetic fields as well as compounds that influence L-type calcium (nimodipine) channels, dopamine D_2 receptors (haldol, chlorpromazine), and glucocorticoid receptors (prednisolone). Nimodipine produced a mild analgesic response that was reduced by exposure to a theta burst pattern and which did not produce analgesia by itself, but is known to produce long-term potentiation in hippocampal slices. The analgesia evoked by the burst-firing field was not reduced by nimodipine. Neither of the D_2 antagonists nor prednisolone produced significant analgesia nor blocked the analgesic effects produced by the burst-firing field.

Keywords Analgesia; Dopamine; Glucocorticoid; Hotplate; Nimodipine; Rat; Weak magnetic stimuli.

Introduction

There is a significant body of literature to suggest that temporally patterned magnetic stimuli can influence measures of endogenous opioids [1], nonopioid stress [2], ionic species [3], fundamental behavioral processes [4], memory acquisition [5], and nociceptive thresholds [2, 6, 7]. It has been suggested that the analgesia induced by a specific temporal pattern of a pulsed magnetic field was mediated via an opioidergic pathway [7]. This pattern is composed of a burst-firing sequence lasting

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Present address: Institute of Medical Science, Medical Science Building Room 3318, University of Toronto, Toronto, Ontario M5S 1A8, Canada.

Address correspondence to M. A. Persinger, Behavioural Neuroscience Laboratory, Laurentian University, Sudbury, Ontario P3E 6B1, Canada; E-mail: mpersinger@laurentian.ca

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690 msec and is presented once every 4 s for 30 min. If the analgesia induced by this magnetic pattern is mediated by the opioid system then the administration of various pharmacological agents shown to modulate opioid induced analgesia should affect the vectorial characteristics of this response. In the present study, we attempted to alter the direction and magnitude of the magnetic field induced analgesia by administering drugs that affect specific chemical systems.

Tail flick latencies are increased significantly when endomorphin-1 and the L-type voltage dependent calcium channel (VDCC) blocker nifedipine are micro injected into the ventral periaqueductal gray of the midbrain [8]. It also has been reported that the combination of a low dose VDCC blocker (N, P/Q, and L) can potentiate morphine induced analgesia when the VDCC blockers are administered spinally [9]. Kavaliers and Ossenkopp [10] have suggested that exposure to magnetic stimuli affects the functioning of calcium channels and the distribution of calcium ions, thereby, altering the effects of opiates.

On the other hand components of the dopamine pathway also influence opioid behaviors. Early studies have indicated that there is lowered analgesia when the dopamine system is activated and enhanced analgesia with dopamine receptor antagonists. The dopamine$_2$ (D_2) receptor agonist quinpirole [11] and dopamine precursor l-3,4-dihydroxyphenylalanine [12] both decreased morphine induced analgesia. The D_2 antagonist (-)-sulpiride potentiated the analgesic actions of the μ-selective opioid sulfentanil, while the D_1 receptor antagonist SCH23390 did not influence the opioid induced analgesia [13]. The effects of transcranial magnetic stimulation have been reported to increase extracellular concentrations of dopamine when applied acutely [14] but not chronically [15]. These reports may suggest that dopamine agents may interact with the analgesia induced by our specific pulsed magnetic field treatment.

There has been considerable evidence that animals subjected to stressful stimuli including footshock [16], swim-stress [17], immobilization and restriction [18], and electroconvulsive shock paradigms [19] have produced an opioid reversible form of analgesia. Recently, it has been demonstrated that morphine exposure induces a cyclic AMP and protein kinase A-dependent upregulation of neuronal glucocorticoid receptors (GR) within the spinal cord dorsal horn [20]. Alternatively, exposure to an extremely-low-frequency oscillating magnetic field with a 37 Hz periodicity similarly reduces the analgesia associated with restraining c57 mice [21]. We hypothesized that if the action of the specific pulsed magnetic fields are opioid mediated or closely related then an interaction with the glucocorticoid system should be apparent.

In the present study, we investigated the influence of 3 seemingly unrelated biological systems (calcium, dopamine, and glucocorticoid) on the analgesia induced by specific magnetic patterns. We were concerned that researchers have focused directly on affecting the opioid system and may not be exploring alternative possibilities. We, then, wanted to determine if pharmacological agents that have been documented to influence opioid-induced analgesia in a very specific manner would change the magnetic field induced analgesia in a similar manner. The effects of the VDCC blocker nimodipine on the levels of analgesia induced by 2 specific complex magnetic patterns were measured. The influence of 2 unrelated receptor systems were also studied. Dopamine antagonists (i.e., haldol and chlorpromazine) and the glucocorticoid agonist prednisolone were administered to potentiate the analgesia induced by the specific magnetic field pattern.

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Methods

Subjects

Eighty-four male albino Wistar rats, between 4 and 10 months of age were employed as subjects in the present experiments. They were obtained from Charles River (Quebec) and had been habituated to a 12:12 L:D cycle (onset between 0700 h to 0800 h) within temperature-controlled rooms (20–22°C) for at least one month before the initiation of the experiments. Rats were monitored daily by experienced Animal Care Technicians. Purina rat chow and water were available *ad libitum*. The rats were maintained, usually 3 per cage, in standard wire cages (40 cm × 24 cm by 18 cm, high) in racks.

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General Procedure

The general procedure consisted of testing male Wistar rats on an Omnitech thermal plate maintained at 55°C. The apparatus (26 cm × 26 cm) was enclosed within a Plexiglas chamber (18 cm high), so the rat could not escape once placed on the thermal plate. A rat was removed from the thermal device immediately after 2 consecutive hind foot licks occurred or a maximum length of 60 s had elapsed to minimize tissue damage. Each rat was tested 3 times on the thermal plate each day for 2 consecutive days. The first trial on the apparatus was the baseline trial. Immediately after the baseline trial a treatment was administered (i.e., injection of a pharmacological agent and exposure to either a magnetic field or sham field for 30 min). Immediately after the termination of the treatment the rat was tested for a second time on the thermal plate, and tested a third time 30 min later (or 30 min after the removal from the field or sham field). This sequence was repeated for 2 consecutive days for each rat.

Experiment 1: The Injection of the L-Type Voltage Dependent Calcium Channel Blocker Nimodipine and Exposure to Two Specific Pulsed Complex Magnetic Patterns. In this experiment, we investigated the possibility that the blockade of the L-type VDCC may influence thermal latencies induced by 2 specific complex magnetic patterns. The first complex pattern was a theta-burst stimulation pattern designed to mimic the firing parameters of hippocampal pyramidal cells during learning. It has been shown to induce strong long-term potentiation (LTP) in hippocampal slices [22]. The pattern consisted of 5 pulsed bursts at 100 Hz separated by 140 msec (i.e., theta rhythm) and was considered because of the dense distribution of the opioid receptors in the hippocampal region [23]. The instrumentation that generated this pattern faithfully reproduced the theta-burst LTP protocol (i.e., 4 stimuli at 100 Hz pulsed at 5 Hz) with a correlation between the electrical signal generated by the computer and the measured magnetic field ranging between 0.9 to 0.98 as reported in a previous publication [24]. The second complex magnetic pattern was a burst-firing pattern [25] modeled after recordings of amygdaloid activity in epileptic patients. All magnetic exposures were intensity-matched (<1 μT) and are represented in Fig. 1. The spatial gradients of the area within which the fields were generated have been published elsewhere [6].

After baseline measurements were taken, nimodipine (5 mg/kg) or physiological saline (0.9%; 1 ml/kg) was injected subcutaneously. This was followed by 30 min

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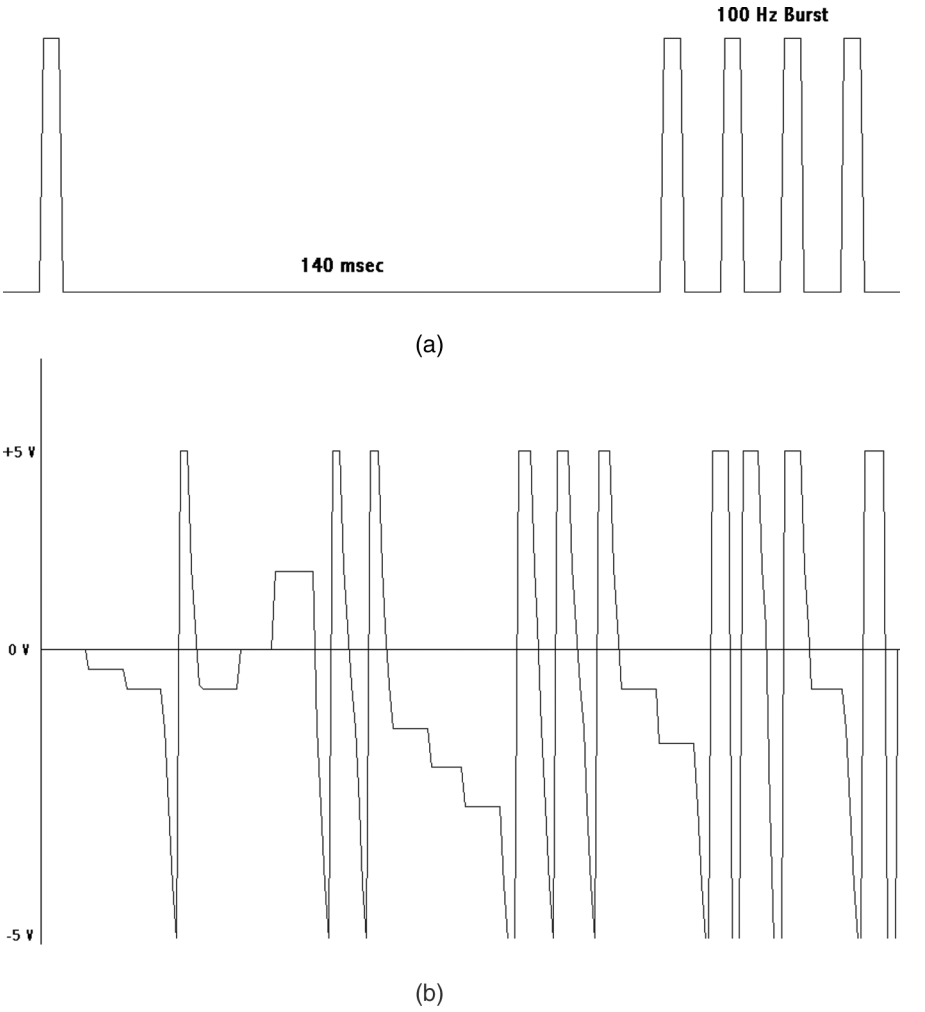

Figure 1. a) The theta-burst stimulation patterned waveform. The sequence consisted of an initial priming pulse followed after 140 msec (theta rhythm) by a 100 Hz burst. b) The structure of the burst-firing magnetic pattern was modeled after recordings of amygdaloid activity in epileptic patients.

exposure to either the burst-firing pattern ($n = 4$/group; nimodipine and saline), theta-burst stimulation ($n = 5$/group), or sham-field conditions ($n = 5$/group). The dosage of nimodipine was selected based on unpublished pilot studies and other observations [26]. Rats were then tested for the appropriate thermal latencies over 2 consecutive days. Both patterns were presented once every 4 s for 30 min.

Experiment 2: The Administration of Dopamine Antagonists and the Analgesia Induced by a Specific Pulsed Magnetic Field. It previously has been demonstrated that dopamine blockers and/or gene knock out mice targeted for the D_2 dopamine receptor significantly potentiate morphine and opioid induced analgesia [27]. In the current study, we reasoned that if stimulation of D_2 receptors potentiated

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morphine analgesia by the same mechanisms as our magnetic field treatment, then antagonists should diminish this interaction. The dopamine antagonists, haloperidol (haldol) (0.4 mg/kg), and chlorpromazine (3 mg/kg), both of which have high binding affinity for the D_2 receptor [28], or physiological saline (0.9%) was injected subcutaneously after baseline measurements were taken on the hotplate (55°C). The rats ($n = 4$/group) were then exposed for 30 min to either a burst-firing magnetic pattern lasting 690 msec presented every 4 s or to the sham-field.

Experiment 3: The Injection of Differing Dosages of a Glucocorticoid Agonist and Exposure to a Specific Pulsed Magnetic Pattern. The inhibitory effects of magnetic field application on stress-induced analgesia have been well documented [29]. We were interested in directly modulating the analgesia induced by the burst-firing pattern by affecting the apparently complex chemical circuitry, often oversimplified by the concept of stress, by administering a glucocorticoid agonist. Either, prednisolone (1, 5, 10 mg/kg) or physiological saline (0.9%; 1 ml/kg) was injected immediately following baseline measurements on the hotplate. There were 4 rats per group.

Statistical Analysis

Multivariate analysis of variance (MANOVA) with 2 levels repeated (day of testing and trials per day) and 2 between subject levels (pharmacological agent injected and magnetic field exposure) was the primary statistical tool. The net differences in response latency (Trial2-Trial1 and Trial3-Trial1) were employed as measures of analgesia to accommodate for individual differences in baseline responding. Increased latencies relative to baseline were considered indicators of increased thermal analgesia. In general, there are no significant differences in analgesic responding between the 2 days of testing; therefore, we chose to combine the data from the 2 days (i.e., the means of the baseline trial were averages, and the means of the subsequent 2 trials were averaged for each trial over the 2 days of testing). Post hoc analysis were completed with Tukey's ($P < 0.05$) test and correlated t-tests where appropriate. All analyses were completed using SPSS software on a VAX 4000 computer. To decrease repetition, only the *statistically significant* ($p < 0.05$) results of the multivariate analysis of variance are presented. Eta-squared values (η^2), or measures of the amount of variance in changes in analgesic responding produced by the treatment were included to indicate effect size.

Results

Experiment 1

The injection of nimodipine (5 mg/kg) significantly increased thermal latencies compared to saline injected controls [$F(1, 22) = 5.57$, $p < 0.05$, $\eta^2 = 20\%$]. The application of the burst-firing magnetic pattern also increased significantly the thermal response times of the rats compared to rats exposed to theta-burst stimulation or sham-field conditions [$F(2, 22) = 4.45$, $p < 0.05$, $\eta^2 = 28\%$]. There also was a statistically significant interaction between the magnetic field treatment and the calcium blocker [$F(2, 22) = 4.58$, $p < 0.05$, $\eta^2 = 28\%$]. Post hoc analysis showed that the primary source of the interaction was due to the attenuation of the

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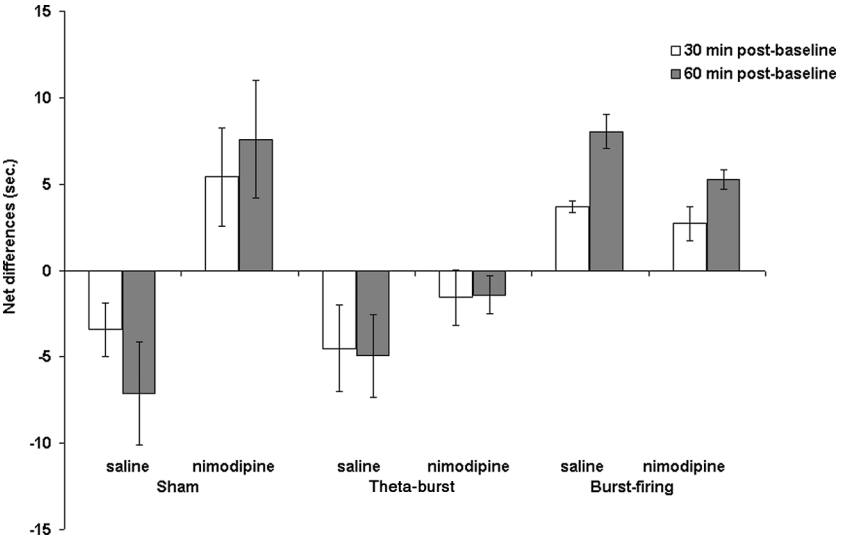

Figure 2. Net changes in thermal response times from baseline on the first day of testing for rats injected with either saline or nimodipine (5 mg/kg) and exposed to either sham conditions or a theta-burst magnetic pattern or a burst-firing magnetic pattern for 30 min. Vertical bars indicate SEMs.

analgesia induced by the nimodipine in the rats exposed to theta-burst stimulation, while the burst-firing magnetic pattern had no apparent influence on the nimodipine treatment. This relationship can be seen in Fig. 2. However, no other interactions or effects were present [all $F < 2.70$].

Experiment 2

Figure 3 displays the mean and SEMs of the thermal latencies for the rats that were exposed to the magnetic field condition (burst-firing vs. sham) and injected with either a dopamine blocker or physiological saline. The application of the burst-firing magnetic pattern significantly increased thermal latencies [$F(1, 18) = 9.04$, $p < 0.01$, $\eta^2 = 33\%$], while the application of the dopamine blockers did not produce an analgesic response [$F(2, 18) = 1.29$, n.s.]. The only significant interaction occurred between the magnetic field treatment and the trial of testing [$F(1, 18) = 7.34$, $p < 0.05$, $\eta^2 = 29\%$]. The thermal latencies were higher 30 min after removal from the magnetic field then immediately after removal from the field. No other interactions or effects reached statistical significance [all $F < 2.70$].

Experiment 3

The injection of prednisolone at 1, 5, or 10 mg/kg did not significantly alter thermal thresholds [$F(3, 24) = 0.13$, $p > 0.05$]. However, the application of the burst-firing magnetic pattern did increase thermal thresholds [$F(1, 24) = 15.57$, $p < 0.01$, $\eta^2 = 39.3\%$]. There were no statistically significant interactions between the 2 treatments [$F(3, 24) = 0.66$, $p > 0.05$]. The means and SEMs of the thermal latencies for the

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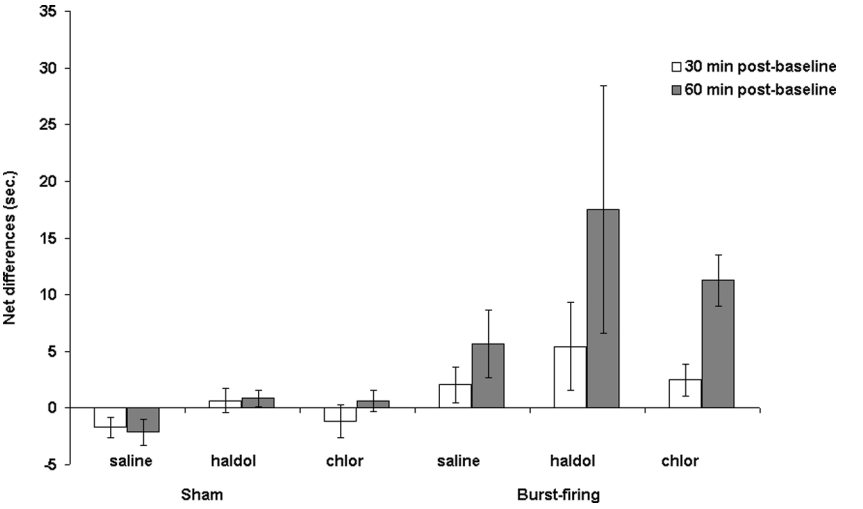

Figure 3. Net changes in thermal response latencies from baseline of animals injected with haldol, chlorpromazine (chlor) or physiological saline and exposed to either sham conditions or the burst-firing magnetic pattern. SEMs are represented.

animals injected with prednisolone and exposed to a magnetic field condition are represented in Fig. 4.

Discussion

A number of studies have suggested that the analgesic properties of specific temporal patterns of magnetic fields can be influenced by endogenous and

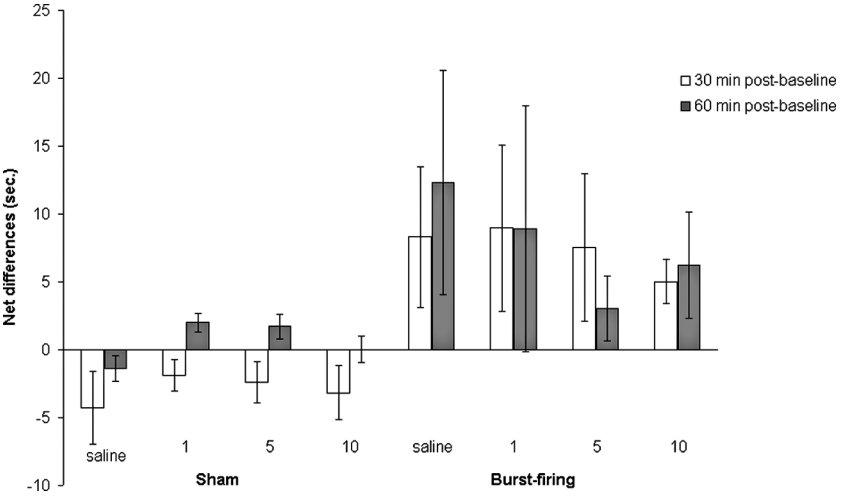

Figure 4. Net changes in thermal responding from baseline are represented for rats injected with either 1, 5, 10 mg/kg of prednisolone or physiological saline, and exposed to either the burst-firing magnetic field of sham field. Vertical bars indicate SEMs.

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exogenous opioids [7, 30, 31]. In this study, we examined the possibility that the analgesia induced by specific pulsed magnetic fields could be influenced by compounds that have been known to alter the analgesia induced by opiate compounds. Kavaliers and Ossenkop [32] have reported that the Ca^{2+} chelator EGTA blocked the daytime and locomotor effects of morphine, while the Ca^{2+} ioonophore A23187 potentiated the inhibitory actions. They have also suggested [10] that exposure to magnetic stimuli affects the functioning of calcium channels and the distribution of calcium ions, thereby, altering the effects of opiates. The L-type Ca^{2+} channel antagonist nifedipine (a dyhydropyridine) reduced inhibitory analgesic effects induced by exposure to a 0.5 Hz rotating magnetic field. In the present study, the analgesic effects of the burst-firing pulse did not interact with the L-type VDCC blocker nimodipine, but an interaction with the theta-burst pattern was evident. Extrapolation from the aforementioned reports and the current study may suggest that Ca^{2+} involvement may be critical for opioid analgesia and magnetic stimuli that possess a similar mechanism.

The administration of nimodipine without a magnetic field treatment elevated thermal thresholds and suggests this drug may have slight analgesic properties. However, exposure to the theta-burst magnetic pattern reduced this mild analgesic effect. Initially theta-burst stimulation was used because it was designed to mimic the firing parameters of hippocampal pyramidal cells and there are vast distributions of μ-opioid receptors in the hippocampal region [23]. Exposure to the same theta-burst magnetic field has been shown to strongly attenuate freezing behaviour during contextual fear conditioning [33], which suggests that the timing of this magnetic pattern hinders the memory process.

However, the injection of nimodipine (5 mg/kg) has been shown to enhance spatial [34] and sequential [24] memory rather than hinder it. One explanation from our results is that the actions of theta-burst-stimulation are mediated through or can be influenced by the L-type VDCC. The theta-burst stimulation may increase extracellular calcium concentrations. We did not expect the theta-burst stimulation to enhance (at least thermal) nociceptive sensitivity. This may be the first evidence that theta-burst magnetic stimulation designed to mimic hippocampal processes may actually increase calcium concentrations and decrease nociceptive thresholds.

Since we were interested in elevating nociceptive thresholds and the analgesic activities of specific patterns of magnetic fields, we chose to use the burst-firing magnetic pattern in our other experiments and determine if its analgesic actions could be influenced by receptor systems known to influence opioid analgesia. The first receptor system we choose was the dopamine receptor system, more specifically the D_2 receptor. We chose the D_2 receptor because it has been shown to greatly enhance morphine and opioid analgesia, while the D_1 receptor did not display these properties [13]. The administration of haldol and chlorpromazine did not enhance analgesia when administered alone. The D_2 blockers did not potentiate the analgesia induced by the burst-firing magnetic pattern. These results are consistent with the conclusion that the analgesia induced by this specific pulsed magnetic pattern is not mediated through a μ-opioid receptor based mechanism. The dosages of the dopaminergic agents were selected based upon the results of our pilot studies as well as the effective dosages as reported by other researchers [35, 36]. It is possible that the dosages employed in this study were not optimal for potentiating the analgesia induced by our specific pulsed magnetic field treatment. It should be noted that when haldol was administered in conjunction with the burst-firing

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magnetic pattern there was increased variability in this group. Often, increased within-group variability due to treatments indicates only the more vulnerable rats were responding to the dose employed. It is unlikely that the analgesia evoked by the specific pulsed burst-firing magnetic pattern is mediated only through an opioid based mechanism. Receptors other than the μ-opioid receptor have been shown to be influenced by dopaminiergic compounds including the σ [37], κ [26], and δ [38] and cannot be ruled out.

Our final attempt to influence the magnetic field induced analgesia was to target the circulating stress hormones since there is considerable evidence to indicate an interaction between stress-induced analgesia and magnetic fields [21]. We chose prednisolone because it is a prominent agonist of glucocorticoid receptors and there had not been any extensive research to indicate the possibility of using this agent to induce analgesia in this area of research despite the usage of synthetic glucocorticoids as treatments for inflammatory induced pain in human populations.

The actions of prednisolone did not appear to be analgesic when administered alone, even at a dose as high as 10 mg/kg, and did not seem to significantly potentiate the analgesia induced by the burst-firing magnetic pattern. This suggests that the analgesic activities of the burst-firing magnetic pattern are not influenced by the drug prednisolone. Glucocorticoids may still play a significant role in the work conducted by Del Seppia and colleagues [21] even though it may not play a role in the analgesia produced by the burst-firing magnetic pulse. Stress hormones such as corticosterone have been shown to be altered in response to magnetic stimuli [39], although the intensity levels were in the order of 200X greater than the ones used in our study.

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